

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
ROBERT J. SMYTH
MORGAN LEWIS & BOCKIUS LLC
1111 PENNSYLVANIA AVENUE, NW
WASHINGTON, DC 20004

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Applicant's or agent's file reference 44508-5008WO		Date of mailing (day/month/year) 17 FEB 2006
FOR FURTHER ACTION See paragraph 2 below		
International application No. PCT/US04/37045	International filing date (day/month/year) 08 November 2004 (08.11.2004)	Priority date (day/month/year) 07 November 2003 (07.11.2003)
International Patent Classification (IPC) or both national classification and IPC IPC(7): A61K 31/19 and US Cl.: 514/557		
Applicant HENRY M. JACKSON FOUNDATION		

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Date of completion of this opinion 14 December 2005 (14.12.2005)	Authorized officer <i>Michel Gratte</i> Michel Gratte Telephone No. (571) 272.1600
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Form PCT/ISA/237 (cover sheet) (April 2005)

Doc. no. 2/24/06 Attorney RTS/RTS/FMK
 Class 044508-5008WO
 Due Date 17 May 06
 Action Written Opinion
 By BIR Chk WS

**WRITTEN OPINION OF THE
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International application No.

PCT/US04/37045

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

- ☐ a sequence listing
☐ table(s) related to the sequence listing

b. format of material

- ☐ on paper
☐ in electronic form

c. time of filing/furnishing

- ☐ contained in the international application as filed.
☐ filed together with the international application in electronic form.
☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☒ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
See the lack of unity section of the International Search Report (Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos. ____

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Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Claims 2,6-15 and 18-33

YES

Claims 1,3-5,16 and 17

NO

Inventive step (IS)

Claims NONE

YES

Claims 1-33

NO

Industrial applicability (IA)

Claims 1-33

YES

Claims NONE

NO

2. Citations and explanations:

Please See Continuation Sheet

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:

Claims 1 and 3-5 novelty under PCT Article 33(2) as being anticipated by LU et al provides evidence that pyruvate regulates hypoxia-inducible gene expression by stimulating the accumulation of hypoxia-inducible Factor 1 alpha 9 in current claim 1, see abstract), that HIF-1 is a key transcription factor that up regulates a series of genes involved in glycolytic energy metabolism, angiogenesis, cell survival and erythropoiesis and that included among the genes are vascular endothelial growth factor (VEGF) and glucose transporters (in current claim 3; see page 23111) and further charges a family of prolyl hydroxylase enzymes with the regulation of the binding of a particular tumor suppressor protein to HIF-1 alpha by hydroxylating key proline residues on the HIF-1 alpha protein (in current claims 4-5; see page 231110.

Claims 16-17 lack novelty under PCT Article 33(2) as being anticipated by US Patent No. 6,222,018 to SEMENZA. SEMENZA teaches a method of treating hypoxia related disorders (in current claim 16, see col. 2, lines 28-30) and that HIF-1 is a mediator of adaptive responses to hypoxia that underlie cellular and systemic oxygen homeostasis (see also col. 14, lines 60-66). That the pyruvate is administered to a pregnant human at risk for premature delivery is a necessary condition of some embodiments of claim 16, that is where for example, proper oxygen homeostasis is not present.

Claims 1-15 and 24-33 lack an inventive step under PCT Article 33(3) as being obvious over LU et al as applied to claims 1 and 3-5 above. Although LU et al do not specifically address the application of pyruvate to humans nor any specific conditions other than cancer or specific modes of administration one of ordinary skill in the art would have found it obvious to treat a patient with pyruvate and modulate hypoxic adaptation by among other mechanisms of action, the induction of angiogenesis (in current claims 11-15; see discussion on page 23115) for cardiac related indications such as heart attack, arrhythmias or smoke inhalation. Additionally obvious to one of ordinary skill in the art would be the modes of administration claimed which include almost every type of administration known, for example, buccal, rectal, via lozenge or cream, as a powder, patch, tablet or suspension and comprising a pharmaceutically acceptable carrier administered repetitively at least once every two days. Particularly because the claimed modes of administration are so exhaustive and that one of ordinary skill in the art would appreciate that the pyruvate needs to be administered somehow, one of ordinary skill in the art would find it obvious to administer the pyruvate as claimed.

Claims 18-23 lack an inventive step under PCT Article 33(3) as being obvious over LU et al as applied to claims 1 and 3-5 above in view of KORITZINSKY et al. KORITZINSKY et al teach that the radiation survival of a hypoxia-treated cell population is lower than for re-oxygenated cells (in current claim 18, see Abstract) which suggests that activation of the HIF-1 alpha gene would protect against the harmful effects of radiation. One of ordinary skill in the art would have found it obvious, absent any indication that modulation of HIF-1 alpha needs to be chronologically coordinated with the administration of radiation, to administer the pyruvate at a time before, after or during radiation particularly because the time frames of before, during and after occupy all the time frames available for the

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

administering of pyruvate proximate to the radiation. Further, one of ordinary skill in the art would have found it obvious to administer the pyruvate at a time somewhat proximate to the administration of the radiation for the pyruvate to stimulate HIF-1 alpha gene expression and protect against the harmful effects of radiation.